REMARKS

Claims 31, 71, 76-82, and 84-93 were pending in the instant application. By this amendment, claims 31, 71, 78- 82, 85, 92 and 93 have been amended in order to clarify the invention and new claims 94-121 have been added to more particularly point out what Applicants regard as the invention. In addition, claims 86 to 90 have been cancelled, without prejudice.

In particular, claims 31 and 71 have been amended to remove the reference to "a heat shock protein fragment," and to add the phrase "in need thereof" to clarify that the compound is administered to a human in need of inhibiting an immune response. Support for the amendment is found at page 9, lines 23-25 and 31. In addition, claim 31 has been amended to replace "modulating" with "inhibiting". Support for the amendment is found at page 9, lines 27-29, and page 49, lines 5-16. The reference to a "first" heat shock protein has also been removed from claim 31 since only one heat shock protein is recited in the amended claim. Claim 78 has been amended to correct the antecedent basis. Claims have been amended to correct the antecedent basis in view of the amendments to claim 31.

Support for the new claims can be found in the specification as follows: support for new claim 94 and 111 is at page 13, lines 25-26; support for new claim 95 and 113 is at page 13, line 36; support for new claim 96 and 114 is at page 51, lines 16-22; and support for new claims 97-101 and 116-120 is at page 54, lines 7-27, and in Figure 3C. Support for new claims 102-106 and 121 is at page 50, lines 1-20. Support for new claim 107 is at page 15, lines 3-6. Support for new claim 108 is found at page 50, lines 1-2. Support for new claim 109 is found at page 50, lines 2-5. Support for new claim 110 is found at page 65, lines 19-21. Support for new claim 112 is found at page 50, lines 7-10. Support for new claim 115 is found at page 50, lines 10-14.

Applicants believe that no new matter has been added by these amendments and new claims.

Accordingly, claims 31, 71, 76-82, 84, 85, and 91-121 will be pending upon entry of this amendment in the instant application. Applicants respectfully request that the amendments and remarks made herein be entered into the record of the instant application.

1. THE REJECTION UNDER 35 U.S.C. § 112, FIRST PARAGRAPH, FOR LACK OF WRITTEN DESCRIPTION, SHOULD BE WITHDRAWN

Claims 31, 71, 76, and 80-91 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors, at the time the application was filed, had possession of the claimed invention. Specifically, the Examiner alleged that the specification fails to provide an adequate written description to support the set of compounds consisting of an alpha (2) macroglobulin ("α2M") fragment, an α2M receptor fragment, and an heat shock protein ("HSP") fragment.

In response to the Examiner's rejection as it relates to an HSP fragment, Applicants note that, without conceding the correctness of the Examiner's rejection and in order to expedite the prosecution of the instant application, claims 31 and 71 have been amended to remove reference to an HSP fragment, and Claims 86-90 have been canceled, thus rendering the rejection moot. In response to the rejection with respect to the α2M fragment and the α2M receptor fragment, Applicants respectfully traverse for the reasons of record which are explained more fully below.

Claim 31 recites, in relevant part, a purified compound selected from the group consisting of an antibody, an α2M fragment, and an α2M receptor fragment, which compound interferes with the interaction of an HSP with the α2M receptor.

Claim 71 recites, in relevant part, a purified compound selected from the group consisting of an antibody and an α2M fragment, which compound binds to the α2M receptor.

Claims 76 and 84 depend from claims 31 and 71 and provide specific embodiments wherein the compound is an antagonist and a peptide.

Claims 80-82, 85, and 91 depend from claim 31 and provide specific embodiments of the HSP and the immune response.

Applicants address the Examiner's rejections with respect to α2M and α2M receptor fragments separately, beginning with α2M fragments. The Examiner asserted at page 3 of the Office Action, that sufficient description was lacking for "which portions of α2M are encompassed as fragments." Applicants maintain that the specification provides sufficient description of the portions of α2M encompassed as fragments to satisfy the requirements of 35 U.S.C. § 112, first paragraph, as set forth in the Guidelines for

Examination of Patent Applications Under the 35 U.S.C. 112 ¶ 1, "Written Description Requirement." 66 Fed. Reg. 1099 (Jan. 5, 2001). See also *Amgen, Inc. v. Chugai Pharma.*, 927 F.2d 1200 (Fed. Cir. 1991); *Fiers v. Revel*, 984 F.2d 1164 (Fed. Cir. 1993).

The Examiner alleged that the specification does not adequately describe the genus of α2M fragments encompassed by the rejected claims. The Examiner asserted at page 3 of the Office Action, that "...the structure of α2M is well established in the art, however, neither the specification or the claims provide sufficient description of which portions of α2M are encompassed as fragments." The Examiner further asserted on page 4 of the Office Action that "no structure function relationship has been made" and that "no structural detail other than the minimum number of amino acids" is disclosed.

In response, Applicants respectfully disagree with the Examiner's characterization of the present disclosure. Specifically, Applicants maintain that the specification provides sufficient description of the genus of α2M fragments by describing twelve representative species and by describing a combination of identifying characteristics of the genus including amino acid sequence structure and functional characteristics that correlate with the sequence structure. For example, the specification provides twelve exemplary α2M fragments, SEQ ID NOS: 8-19, at page 51, lines 16-22. The specification also provides the specific portions of α2M that interact with the α2M receptor, namely amino acids 1314-1451, described at page 13, lines 27-29, Fig. 7B, and in the references provided at page 3, line 34 through page 4, line 7, including Salvesent *et al.*, 1992, FEBS lett. 313:198-202 and Holtet *et al.*, 1994, FEBS Lett. 344:242-246. Finally, the specification teaches that there is an art-recognized correlation between the structure of the α2M receptor-binding domain identified in Figure 7B and the functional ability of α2M to bind to the α2M receptor. Specifically, at page 4, lines 8-13, the specification provides that an "alignment of α2M receptor ligands identifies a conserved domain" which "spans amino acids 1314-1451 of human α2M" and that two of those conserved residues are required for binding to the α2M receptor, as demonstrated by Nielson et al., 1996, J. Biol. Chem. 271:12909-912. Accordingly, appropriate written description is provided for the α2M fragments of claims 31 and 71.

In summary, the specification provides *twelve* specific examples of the genus of α2M fragments encompassed by the claims. The specification further provides distinguishing attributes of the genus, e.g., the specific portion of the α2M protein from

which the fragments are derived and an art-recognized correlation between the structure of that portion of the α2M protein and the function of binding to the α2M receptor. Accordingly, Applicants maintain that the written description requirement of 35 U.S.C. § 112, first paragraph, is satisfied with respect to the genus of α2M fragments recited in claims 31 and 71.

The Examiner also alleged that the specification does not adequately describe the genus of α2M receptor fragments encompassed by claim 31. The Examiner asserted at page 4 of the Office Action, that "the disclosure of a single species does not adequately represent" the genus. The Examiner further asserted that "no structure function relationship has been made" and that "no structural detail other than the minimum number of amino acids" is disclosed.

In response, Applicants respectfully disagree with the Examiner's characterization of the present disclosure. In particular, Applicants point out that the specification provides *eight* exemplary α2M receptor fragments, namely, three corresponding to SEQ ID NOS: 20-22 (see page 54, lines 15-27, of the specification), four corresponding to SEQ ID NOS: 54-57 (see page 73, lines 13-19, page 13, lines 5-9, and Fig. 3C of the specification), and the p80 α2M receptor fragment. SEQ ID NOS: 20-22 are within the CI cluster of the α2M receptor, and are fragments of p80. SEQ ID NOS: 54-57 are located between the CI and CII clusters, and are fragments of p80. The p80 fragment corresponds to an N-terminal fragment of the α2M receptor which includes the CI cluster and additional sequence between the CI and CII clusters (see page 73, lines 13-19, and Figure 8B of the specification). The specification also teaches that the p80 fragment binds to the heat shock protein gp96 (see page 71, line 34 to page 73, lines 1-12, and page 75, lines 1-28, of the specification). Applicants maintain that in view of the evidence of binding between the heat shock protein gp96 and the p80 fragment, a reasonable expectation exists that α2M receptor fragments comprising sequence derived from the p80 fragment will interfere with the interaction of an HSP with the receptor, as specified by claim 31. Such fragments are exemplified by p80 itself and the seven additional sequences recited above.

The specification also provides distinguishing attributes of the fragments which comprise HSP-binding portions of the α2M receptor, *e.g.*, at page 54, lines 7-15, and in Figure 8B. For example, the specification provides that the HSP-binding portion of the α2M receptor consists of, or comprises, at least one complement repeat or a cluster of complement

repeats, preferably CI-II. The specification also provides structural details as to the length of the HSP-binding fragment of the α2M receptor, e.g., that it can consist of at least 10, 20, 30, 40, or most preferably 80 amino acids; or that such fragments are not larger than 40-45 or 80-90 amino acids. Finally, the specification describes a particular embodiment of an α2M receptor fragment, namely an 80 kDa fragment, which binds to the heat shock protein gp96 and inhibits the re-presentation of gp96 by antigen presenting cells (see e.g., the specification at page 71, lines 34-37 to page 73, line 28, and the portion of the α2M receptor sequence highlighted in bold in Fig.8B, corresponding to amino acid residues 327-346, described at page 14, lines 2-3).

In summary, the specification provides *eight* exemplary α2M receptor fragments as well as a correlation between the structure of these fragments and HSP-binding, provided by the specific example of the p80 fragment. The specification further provides distinguishing attributes of the genus, e.g., the specific portion of the α2M receptor protein from which the fragments are derived, their preferred length, and an art-recognized correlation between the structure of that portion of the α2M receptor protein and the ligand-binding function of the α2M receptor.

Applicants maintain that it would be apparent to one skilled in the art, at the time the application was filed, that Applicants had possession of the claimed methods for modulating an immune response using (1) an α2M fragment or an α2M receptor fragment that interferes with the interaction between a heat shock protein and the α2M receptor, and (2) an α2M fragment that binds to the α2M receptor.

In view of the foregoing arguments and amendments, Applicants respectfully request the Examiner's withdrawal of the rejections under 35 U.S.C. §112, first paragraph.

2. THE REJECTION UNDER 35 U.S.C. § 112, FIRST PARAGRAPH, FOR LACK OF ENABLEMENT SHOULD BE WITHDRAWN

Claims 31, 71, and 76-93 have been rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to allow one skilled in the relevant art to which it pertains to make and/or use the invention commensurate in scope with the claims.

The Examiner continues to base this rejection on his view that the claimed methods of inhibiting or modulating an immune response are not enabled by the cell-based assays provided in the specification. Specifically, the Examiner continues to assert that there

is insufficient evidence to extrapolate the results from such *in vitro* assays to expected results *in vivo*. The Examiner has maintained this rejection notwithstanding Applicants having provided evidence in their previous response demonstrating a correlation between the results of *in vitro* assays, such as the re-presentation assay described in the specification, e.g., at page 72, lines 29-37, to page 73, lines 1-28, and the inhibition of an immune response *in vivo*. In particular, Applicants provided the Examiner with two references demonstrating a correlation between the ability of an anti-CD91 antibody to block re-presentation of an HSP-peptide complex *in vitro* with inhibition of the protective immunity otherwise elicited by the HSP-peptide complex *in vivo* (see Binder and Srivastava, 2004, Proc. Natl. Acad. Sci. U.S.A. 101:6128-6133; and Binder *et al.*, 2002, Cancer Immunity 2:16-24). The Examiner did not question the sufficiency of the evidence to demonstrate a reasonable correlation between the results of the *in vitro* assays and the modulation or inhibition of an *in vivo* immune response. Instead, Applicants understand the Examiner's continued rejection to be based on the Examiner's view that Applicants' use of post-filing date evidence to support enablement at the time of filing was improper.

In response, Applicants respectfully disagree with the Examiner's position and submit that their use of post-filing evidence to demonstrate enablement at the time of filing was proper. The court in *In re Brana* accepted post-filing evidence provided by the applicants in support of enablement as sufficient to overcome a rejection for lack of enablement. See *In re Brana*, 51 F.3d 1560, 1567 n.19 (Fed. Cir. 1995)("Enablement, or utility, is determined as of the application filing date."; a post-filing date declaration setting forth test results substantiating utility "pertains to the accuracy of a statement already in the specification. ... It does not render an insufficient disclosure enabling, but instead goes to prove that the disclosure was in fact enabling when filed (*i.e.*, demonstrated utility)").

Applicants presented post-filing evidence that the *in vitro* results described in the specification, e.g., the ability of a compound to bind to α2M receptor or to interfere with the re-presentation of an immunogen (a gp96-chaperoned antigenic peptide), are reasonably predictive of the ability of the compound to modulate similarly an immune response *in vivo*. The cell-based re-presentation assay described in the specification was well established in the art at the time of filing, as evidenced in the specification by the reference at page 71, lines 14-15, to Suto and Srivastava, *Science*, 1995 269:1585-88 ("Suto")(submitted in Applicants' earlier filed Information Disclosure Statement as reference no. "CL"). Moreover, as

demonstrated by Suto, the state of the art in 1995 already demonstrated a correlation between the ability of HSP-peptide complexes to stimulate cytotoxic T-lymphocytes ("CTL") in an *in vitro* re-presentation assay with the ability to elicit a CTL response *in vivo* (see e.g., Figs. 1, 3A and 3B, and accompanying text at pages 1586-87 of Suto). Accordingly, Applicants maintain that the ability of a compound to modulate a CTL response in an *in vitro* re-presentation assay was accepted in the art at the time of filing as reasonably predictive of the ability to modulate similarly an *in vivo* immune response. 35 U.S.C. § 112 requires no more. See *Fujikawa v. Wattanasin*, 93 F.3d 1559, 1564 (Fed. Cir. 1996)(stating that the results of *in vitro* tests are sufficient to meet the written description requirement as long as they are reasonably correlated with a pharmacologically useful *in vivo* response).

In view of the results of the *in vitro* assays provided in the specification and the art-recognized correlation between such *in vitro* results and the ability to modulate or inhibit an immune response *in vivo*, as demonstrated by Suto and Srivastava, 1995, by Binder *et al.*, 2002, and by Binder and Srivastava, 2004, Applicants maintain that one skilled in the art, following the teachings of the specification, would be able to identify and use an antibody, an α2M fragment, and an α2M receptor fragment to successfully interfere with the interaction of an HSP and the α2M receptor or to bind to the α2M receptor, and thereby modulate an immune response.

In view of the foregoing arguments and amendments, Applicants respectfully request the Examiner's withdrawal of the rejections under 35 U.S.C. § 112, first paragraph.

3. THE REJECTION UNDER 35 U.S.C. § 112, SECOND PARAGRAPH SHOULD BE WITHDRAWN

The Examiner rejected claims 76 and 84 under 35 U.S.C. § 112, second paragraph, as allegedly indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. Specifically, the Examiner alleged that claims 76 and 84 fail to further limit claims 31 and 71 from which they depend.

In response to the Examiner's rejection, Applicants respectfully traverse and submit that the set of compounds recited in claims 31 and 71 is further limited by dependent claims 76 and 84.

Claim 31 recites, in relevant part, a purified compound selected from the group consisting of an antibody, an α2M fragment, and an α2M receptor fragment, which compound interferes with the interaction of an HSP with the α2M receptor.

Claim 71 recites, in relevant part, a purified compound selected from the group consisting of an antibody and an α2M fragment, which compound binds to the α2M receptor.

Claim 76 limits the "compound" recited in claim 31 or 71 to "an antagonist" which decreases α2M receptor activity.

Claim 84 limits the "compound" recited in claim 31 or 71 to a "peptide."

The plain language of claim 76 limits the set of compounds which interferes with the interaction of an HSP with the α2M receptor of claim 31 to "an antagonist" which decreases α2M receptor activity. There is no requirement in claim 31 that the compound be an antagonist which decreases α2M receptor activity. Instead, claim 31 requires only that the compound interfere with the interaction of an HSP with the α2M receptor. Such a compound is not necessarily an antagonist that decreases α2M receptor activity. In fact, such a compound could be an agonist of α2M receptor activity. For example, a compound such as an activating antibody may trigger signaling from the receptor just as ligand binding does. Accordingly, claim 76 further limits the scope of the set of compounds recited in claim 31 and is properly dependent therefrom. Similarly, there is no requirement in claim 71 that the set of compounds recited in the claim be antagonists which decrease α2M receptor activity. Claim 71 specifies that the compound binds to the α2M receptor. Not all compounds that bind to the α2M receptor are antagonists of the receptor activity. Accordingly, claim 76 further limits the scope of the set of compounds recited in claim 71 and is properly dependent therefrom.

The plain language of claim 84 limits the set of compounds of claims 31 and 71 to a "peptide." This further limits the claims because, for example, there is no requirement in claim 31 or 71 that the antibody be a peptide. For example, a classical immunoglobulin is not a peptide. Accordingly, claim 84 further limits the scope of the set of compounds recited in claims 31 and 71 and is properly dependent therefrom.

In view of the foregoing arguments and amendments, Applicants respectfully request the Examiner's withdrawal of the rejections under 35 U.S.C. § 112, second paragraph.

CONCLUSION

Entry of the foregoing amendment and remarks into the record of the above-identified application is respectfully requested. Applicants submit that the remarks and amendments made herein now place the claims in condition for allowance. If any issues remain in connection herewith, the Examiner is respectfully invited to telephone the undersigned to discuss the same.

Please charge any required fee to Jones Day Deposit Account No. 50-3013. A duplicate of this sheet is enclosed for accounting purposes

Respectfully submitted,

Date: June 9, 2005

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